Integrated Hypothesis of Schizophrenia

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Different Hypotheses of Schizophrenia

Dopamine Hypothesis of Schizophrenia

- Hyper Activity of D2 Receptors
- level of affinity of a drug to D2 and efficacy in reducing psychosis
- Amphetamine Induces Psychosis
- Genetic Studies (COMT, DRD4, and AKT1)
- PET Studies: D2 receptors blocked, psychosis was not reduced.
- D2 receptors are blocked within few minutes but it takes several weeks until some improvement is observed.

Serotonin Involvement

- 5-HT-2A Receptors Agonists (LSD)
- Atypical Antipsychotics

Glutamate Hypothesis of Schizophrenia

- NMDA Receptor Antagonists(PCP, Ketamine)
- Mice with decreased NMDA receptor activity showed symptoms of schizophrenia.
- Influence of D-serine NMDA receptor neuromodulator(agonist).

Excessive Release of Glutamate

- Damage and deterioration of cortical neurons, enlarged ventricles and extensive atrophy are attributed to glutamate toxicity
- Drug that decrease the amount of glutamate in the synapses found to have an antipsychotic effect (LY2140023).

Integrated Hypothesis of Schizophrenia

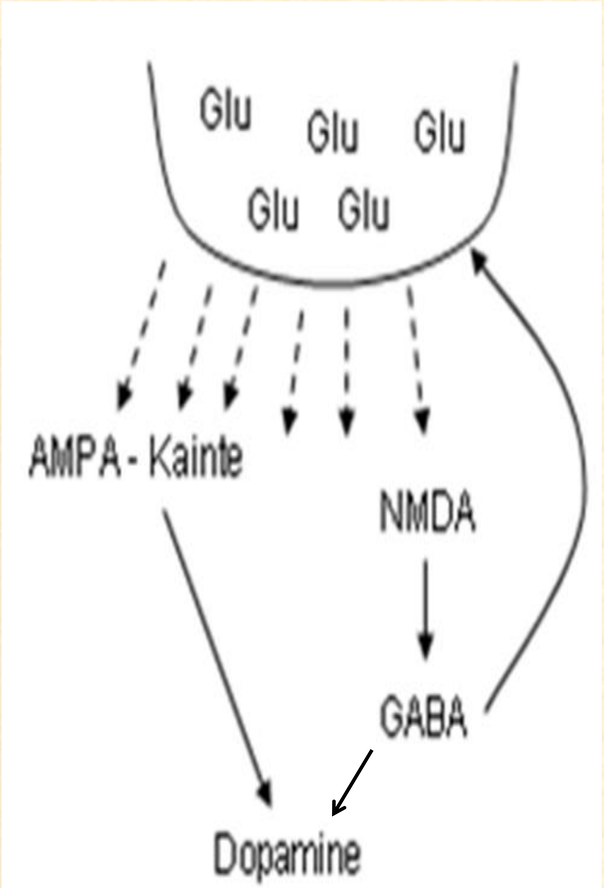
The purpose is to integrate all of this different hypotheses of schizophrenia under one connected biochemical mechanism. To find the mechanism that is responsible for all of these different findings.

Hypo function of NMDAR is a central component of this hypotheses.

- NMDAR hypo function mediated by hypo activity of GABAergic neurons leads to hyper activity of dopaminergic neurons in the VTA and increased release of dopamine in the limbic system.
- NMDAR hypo function mediated by hypo activity of GABAergic neurons leads to hyper activity of glutamatergic neurons and the excessive release of glutamate
- Glutamate in excess binds to non NMDA receptors of glutamate, such as AMPA and Kainate receptors which lead to an increased activity of dopaminergic neurons in the VTA and increased release of dopamine in the limbic system.

How can this Hypothesis be Proven or Refuted?

Evidence that AMPA agonists increase the levels of dopamine in the brain. Not investigated in the context of schizophrenia or with animal models of schizophrenia.



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